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Controllable synthesis, structures of amidecrownophane-type macrocycles and their binding ability toward anions

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Abstract

Amidecrownophane-type macrocycles with different number of hydroxy groups were prepared in quantitative yields by control of the conditions of thermal reaction with the aim to examine the role of hydroxy groups in anion recognition. It was proved that the hydroxy group played a critical role in anion binding for this type of macrocycles and the anion binding affinity could be tuned by different number of hydroxy groups. Further exploration clarified the presence of intramolecular hydrogen-bonding and exhibited the major effect on their anion binding potential.

Macrocycles containing multi-hydrogen bonding sites have gained considerable attention due to their ability of complexation toward ionic and/or neutral molecules.[1] Among these hydrogen bonding motifs, hydroxy groups, however, are surprisingly less explored compared to amine or amide groups, in spite of its strongly hydrogen donating ability and readily functionalized nature.[2,3] In fact, many naturally occurring anion-binding processes involve the cooperative work of the amide N–H and hydroxy groups.[4] Therefore, examination on the role of hydroxy group in anion recognition will provide valuable information to design more efficient receptors for anions. It is well known that the development of strong and selective anion artificial receptors is of great interest and of significance due to the crucial importance of anions in many essential chemical and biological processes.[5]

More recently, we developed a novel and effective synthetic method for amidecrownophane-type macrocycles, in which di(acid chloride) containing isobutenyl moiety reacted with diamine derivatives under normal conditions to give the corresponding macrocycles in high yields.[6] Then, tandem Claisen rearrangement (TCR),[7] an excellent method to introduce hydroxy groups into acyclic and/or cyclic molecules, was carried out to yield macrocycles having two hydroxy and two amide groups. It could be a suitable model to bind anions through the cooperative work of plural hydroxy and amide groups.

In the present work, to examine the role of hydroxy groups in anion recognition, we report the successful synthesis of amidecrownophane-type macrocycles with different number of hydroxy groups via control of the thermal reaction conditions. The anion binding behaviors of these macrocyclic receptors are also investigated by utilizing fluorescence spectroscopy.

The synthetic route for these macrocycles is shown in Scheme 1. The generation of macrocyclic polyether **1** was accomplished by our recently reported procedures[6] in about 80% yield. Then, TCR reaction was carried out by heating polyether **1** (in NMP, 160 °C, 45 min) under argon atmosphere to give macrocycle **2** in quantitative yield. However, when polyether **1** was heated without solvent (170 °C, 1 h) under vacuum, macrocycle **3** was also obtained in quantitative yields. By analyzing the structures of macrocycles **2**, and **3**, we inferred that the origin of

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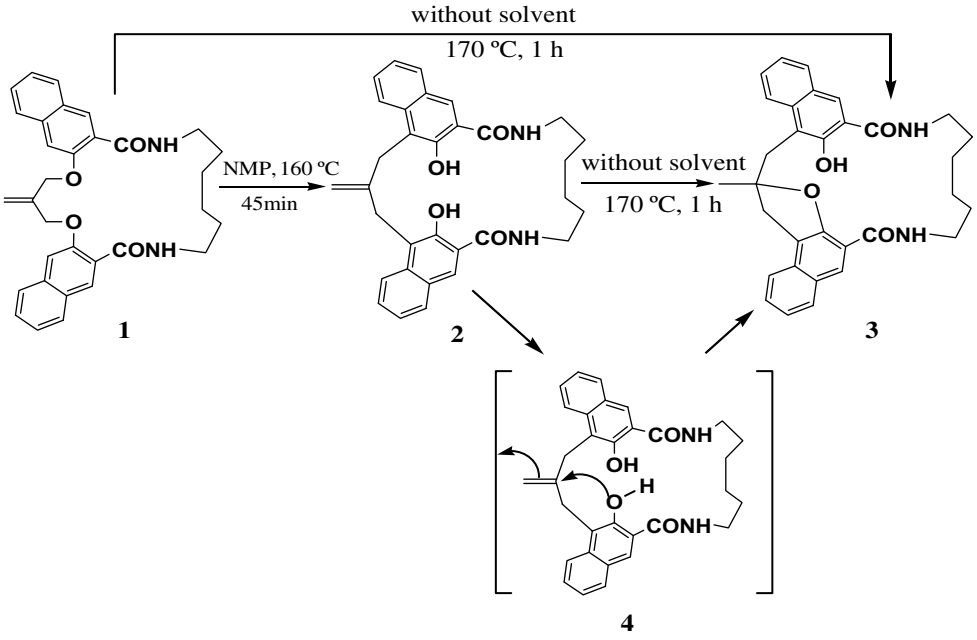

Scheme 1. Synthetic route to amidecrownophane-type macrocycles.

macrocycle **3** might be the intramolecular Michael addition of one of hydroxy groups to isobutenyl methylene moiety in macrocycle **2**, as shown in Scheme 1. This hypothesis was further confirmed by directly heating macrocycle **2** without solvent (170 °C, 1 h) under vacuum to yield macrocycle **3** as the only product.

The solid-state structures of macrocycles **1**–**3** were conformed by single crystal X-ray diffraction studies (Fig. 1).[8] The crystals suitable for X-ray analyses were obtained through slow diffusion of hexane to the chloroform solution containing the above macrocycles. As shown in Figure 1, macrocyclic polyether **1** adopted nearly symmetrical conformation with C=C bond of isobutenyl group inside into the cavity on account of the presence of intramolecular hydrogen bonding between hydrogen on C=C and ether oxygen atom. In contrast, as for macrocycle **2**, after TCR it had to adopt a twisted conformation due to the steric hindrance between the two hydroxynaphthalene rings. The isobutenylene unit is not long enough as a linker to allow the two hydroxy groups to become coplanar, just as shown in Figure 1, two hydroxy groups are both outside of the cavity to give rise to a bowl-like macrocycle. However, in solution phase, no indication of such twisted conformation was observed from ^{1}H NMR spectra (Supplementary data), probably owing to the rapid conformational change at room temperature.[9] As far as macrocycle **3** is concerned, it adopted completely unsymmetrical conformation since the intramolecular Michael addition induced the formation of chiral carbon atom, which was also proved by the appearance of two sets of signals due to the unsymmetrical change of the structure and disappearance of isobutenyl double bond signal from its ^{1}H NMR spectrum. It could be expected that the differences not only in the number of hydroxy groups but also in the conformations between them would induce the subtle change of their ability to bind anions.

To examine the role of hydroxy groups, anion binding behaviors of amidecrownophane-type macrocycles **1**–**3**

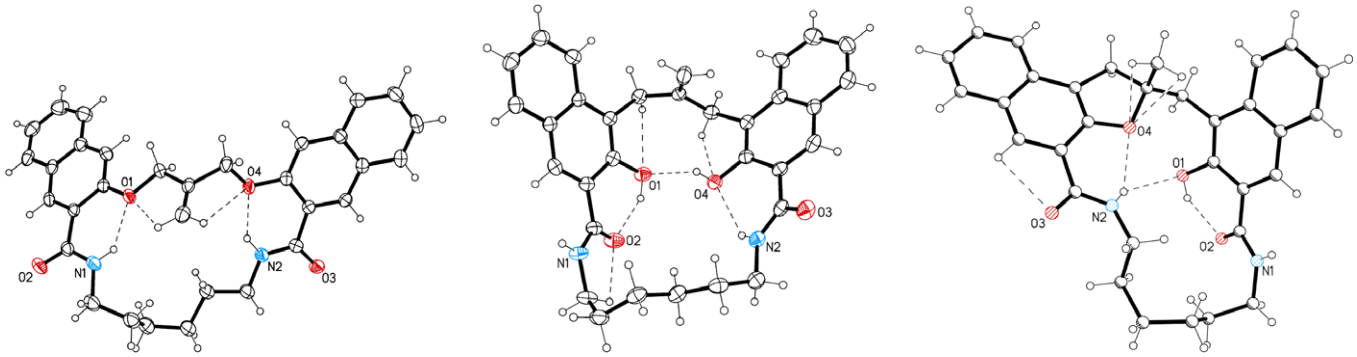

Fig. 1. Crystal structures of synthesized macrocycles **1** (left), **2** (middle), and **3** (right).

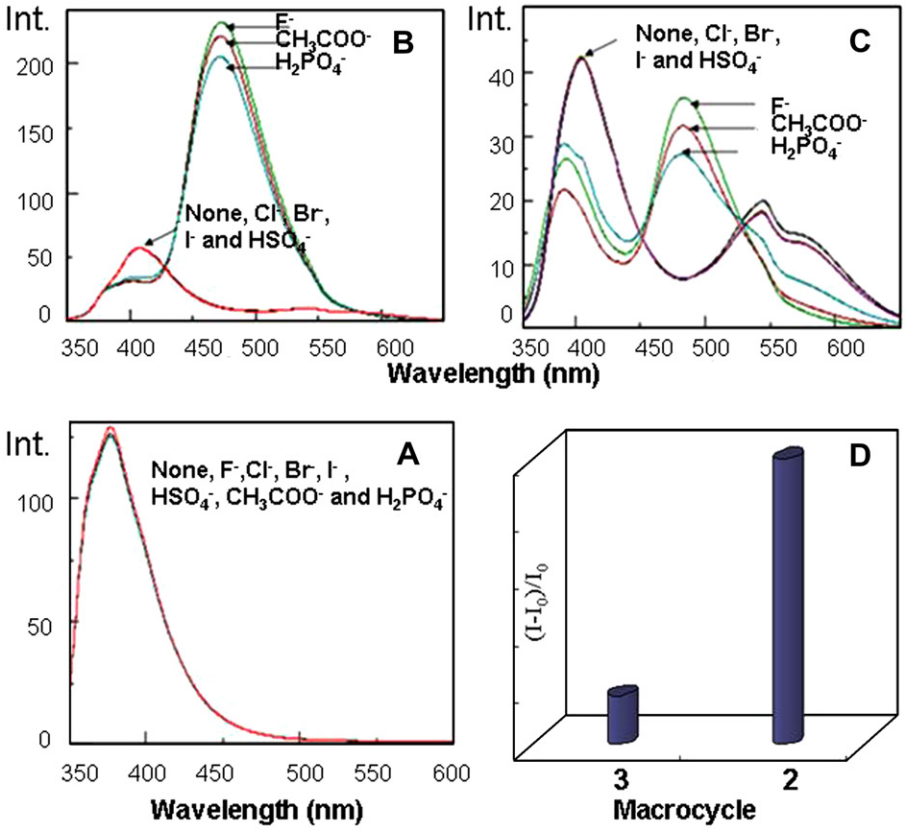

Fig. 2. Changes in fluorescence spectra of macrocycles **1** (A), **2** (B), and **3** (C) upon the addition of various anions and the fluorescence ratio of macrocycles **2** and **3** upon the addition of $\mathbf{F}^-$ (D). $[c]_{Receptors} = 2 \times 10^{-5}$ M, in CH_3CN, 1 equiv anions were added.

were investigated by using fluorescence spectroscopy. The results are shown in Figure 2. As can be seen from this figure, the three macrocycles exhibit different anion recognition abilities. Macrocycle **1** has no binding ability toward any anions due to the absence of hydroxy group in spite of the existence of two amide groups (Fig. 2A), which indicate that hydroxy group plays a crucial role in anion recognition for this type of macrocycles. By contrast, as for macrocycles **2** and **3**, although they both have the ability to respond to F^-, CH_3COO^-, and $H_2PO_4^-$, they exhibit significant difference in changing fluorescent intensity on complexation. For instance, among halides, both of the two macrocycles exhibit fluoride selectivity by the appearance of new peaks at 474 nm (for **2**) and 482 nm (for **3**), together with the quenching of original peaks. On the basis of the previously reported similar cases,[10] the appearance of these new peaks is due to the excited-state proton transfer in the sensor-anion complexes. It is worth noting that macrocycle **2** shows much higher fluorescent sensitivity on complexation with fluoride compared to macrocycle **3**, which can be seen clearly from Figure 2D. It displays the fluorescence ratio $(I-I_0)/I_0$ difference between macrocycle **2** and **3** upon the addition of F^- under the completely same conditions. More interestingly, fluorescence titration experiments pointed to 2:1 stoichiometry between macrocycle 2 and fluoride, and 1:1 binding mode between macrocycle 3 and fluoride (Supplementary data). These results prove our above expectation that the differences not only in the number of hydroxy groups but also in the conformations between these macrocycles would induce the subtle change of their ability to bind anions.

However, it was also observed from Figure 2 that not only F^-, but also CH_3COO^- and $H_2PO_4^-$ can interact with both macrocycles **2** and **3**. Other anions with relatively lower basicity cannot interact with two macrocycles. These results indicate that the hydroxy group in this type of macrocycle is too acidic to discriminate the difference in basicity between F^-, CH_3COO^-, and $H_2PO_4^-$ and has no ability to bind other anions having lower basicity. By further exploration on the structural characters of macrocycles **2** and **3**, we inferred that the intramolecular hydrogen bonding between hydroxy group and carbonyl group might be the reason to inhibit the role of hydroxy group as a normal hydrogen bond donor by increasing its acidic property. It is clear from the single crystal of macrocycles **2** and **3** that the C=O group of amide can form a hydrogen bonding with phenolic hydroxy groups constituting a stable six-membered ring (Fig. 3).

On the other hand, there is also solution-phase evidence for the existence of this intramolecular hydrogen bonding. In CD_3CN solution, the O–H chemical shifts of **2** and **3** were observed in the ^1H NMR spectra at ca. 11.8 and 11.9 ppm, respectively (Fig. 4). This strongly downfield shifted O–H proton indicates the strongly deshielded

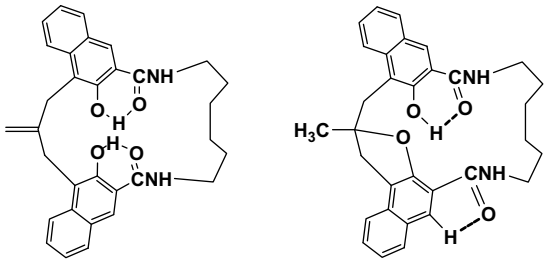

Fig. 3. Intramolecular hydrogen bonding pathway proposed for macrocycles **2** (left) and **3** (right).

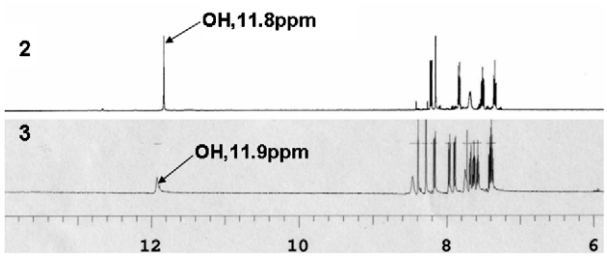

Fig. 4. ^{1}H NMR spectra of macrocycles **2** and **3** in CD_3CN.

environment and strong acidity of hydroxy group, consistent with the presence of intramolecular hydrogen bonding in solution. Therefore, the function of hydroxy group in this type of macrocycles as a normal hydrogen bond donor was inactive and their role as an acid was amplified owing to the existence of strong six-membered intramolecular hydrogen bonding.

In conclusion, we have successfully synthesized the amidecrownophane-type macrocycles with different number of hydroxy groups in quantitative yields via elaborate control of the thermal reaction conditions. The investigation on their anion binding behaviors proved the critical role of hydroxy group for this type of macrocyclic receptors. X-ray and ^{1}H NMR analyses indicated that the presence of intramolecular hydrogen bonding in this type of macrocycles inhibited the function of hydroxy group as a normal hydrogen bond donor and amplified the role of its acid properties. On the basis of these results, in future work, we aim to construct anion receptors in which the linkers will be connected to avoid the formation of strong intramolecular hydrogen bonding.

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Supplementary data

^{1}H NMR spectra of macrocycles **1**–**3**, fluorescent titration of macrocycle **2** and **3** with F^-, as well as the detailed single X-ray data are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.019.

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